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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/020,721	12/14/2001	Motonao Nakao	HIRA.0054	9615

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EXAMINER
CHUNDURU, SURYAPRABHA

ART UNIT	PAPER NUMBER
1637	

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DATE MAILED: 04/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/020,721	NAKAO ET AL.	
	Examiner	Art Unit	
	Suryaprabha Chunduru	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 January 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2 and 4-6* is/are pending in the application.

4a) Of the above claim(s) *5 and 6* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2 and 4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants' response to the office action filed on January 5, 2004 has been entered and considered.

2. Claims 2 and 4-6 are pending. Claims 5-6 are withdrawn in view of restriction, in the previous office action.

Response to arguments

3. Applicants' response to the office action is fully considered and found persuasive in part.

4. With reference to the rejection maintained in the previous office action under 35 USC 102(b) as anticipated by Schollen et al., Applicant's arguments and amendment with respect to claims 2-4 have been considered and found not persuasive. Applicants' argue that the primers for PCR in table 1 of the Schollen et al. reference are different from the oligonucleotide sequences used for hybridization. This argument is fully considered and found not persuasive because on page 20 (column 1, lines 1-6 under the sub title test samples) of the Schollen et al. discloses that the oligonucleotide (RDB) is used as a PCR primer along with the biotinylated PCR primer for amplification of wild-type and mutant-type PCR fragments, and on page 19, the same RBD oligonucleotides were used as hybridization probes (see page 19, column 2, lines 6-16). However, Applicants' amendment, incorporating the limitation (intercalating dye) obviate the rejection, therefore the rejection is withdrawn herein.

5. With reference to the rejection made in the previous office action under 35 USC 103(a) as being unpatentable over Patinen et al. in view of Hawkins, Applicants arguments are fully considered and the rejection is with drawn herein in view of Applicants' arguments regarding no teaching of PCR primers used as probes for hybridization.

6. The following is the rejection made in the previous office action under 35 USC 103(a):

A. Claims 2 and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schollen et al. (Clin Chem, vol. 43, No. 1, pages 18-23, 1997) in view Hawkins (USPN. 6,589,778).

Schollen et al. teach a method of instant claim 2, of detecting PCR-amplified base sequences wherein Schollen et al. disclose that the method comprises (i) conducting PCR amplification by mixing a plurality of pairs of primers with a sample (see page 19, column 1, paragraph 3), said primers being suitable for amplifying different base sequences of a same or different lengths by PCR (see page 19, Table 1, see fragment lengths); (ii) conducting a hybridization reaction by using a substrate on which one primer (RBD primer used as a PCR primer) of each said PCR primer pairs are fixed, and a hybridization solution containing said PCR amplified sequences (see page 19, column 1, paragraph 3, column 2, paragraph 1); detecting the hybridization spot on the substrate in which hybridization reaction occurred by processing the entry of the fluorescent material using chemiluminscent kit (see page 19, column 2, paragraph 1). Schollen et al. also disclose the oligonucleotides on the substrate are equivalent to the PCR primers used in the amplification (see page 20, paragraph 1, column 2, paragraphs 1-4). With regard to the instant claim 4, Schollen et al. teach that the said PCR primers comprise a base length number ranging from 10-30 (see page 19, table 1, page 20, table 2). Although Schollen et al. teach a fluorescent reagent for detection Schollen et al. did not teach an intercalating agent as a fluorescent material.

Hawkins teach a method of claim 2 of detecting a target nucleic acid comprising a detecting at least one of the spots on said substrate (biochip) in which the hybridization reaction

occurs, by processing an intercalating dye to enter in said target molecules comprising double-stranded DNA and detecting fluorescence by exciting said intercalating dye contained in said at least one of the spots on the substrate (biochip) (see column 10, lines 64-67, column 11, lines 1-8).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the method of detecting PCR-amplified base sequences as taught by Schollen et al. with the teachings as taught by Hawkins which is applicable to use intercalating dye as a fluorescent material in signal detection process because Hawkins states that 'detection of hybridization signals by fluorescence is preferred using labeled target molecules or by including intercalating dyes in the hybridization fluid (see column 10, lines 64-67). An ordinary practitioner would have been motivated to combine the method of Schollen et al. with the teachings of Hawkins for the advantages of developing a cost-effective method for detecting PCR-amplified base sequences by including the intercalating dye as a fluorescent material in hybridization reaction because such limitation would reduce the use of expensive fluorescent labeling material in the detection of a target nucleic acid molecule.

Response to arguments:

With reference to the above rejection, Applicants' arguments and amendment are fully considered and found not persuasive. As discussed above in response to the arguments for the rejection under 35 USC 102(b), Schollen et al. teach every limitation in the instant claims. However, to address the fluorescent signal generated from a hybridization event (that is hybridization between double-stranded PCR fragment with an oligonucleotide primer on a substrate), Applicants' arguments are found not persuasive. With regard to Applicants' particular

argument, that the use of intercalating dye excludes the need to label amplicons is a well established fact in the field of molecular biology and there is no need for combining references. This argument is fully considered, however, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir.1992).

Applicants further argue that the use of intercalating dye to detect hybridization products are an unexpected result, and it eliminates the synthesis of fluorescent-labeled probes. This argument is fully considered. However, as MPEP 716.02 (d) states "Whether the unexpected results are the result of unexpectedly improved results or a property not taught by the prior art, the "objective evidence of nonobviousness must be commensurate in scope with the claims which the evidence is offered to support." In other words, the showing of unexpected results must be reviewed to see if the results occur over the entire claimed range. In re Clemens , 622 F.2d 1029, 206 USPQ 289, 296 (CCPA 1980)". Here, the unexpected result- use of intercalating dye is not commensurate in scope with the claim, which is drawn to a known fact that detection of fluorescence signal from an intercalating dye entering PCR-amplified double-stranded DNA. Thus the rejection is maintained herein.

New rejections

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 2 and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schollen et al. (Clin Chem, vol. 43, No. 1, pages 18-23, 1997) in view of Wittwer et al. (US 6,232,079).

Schollen et al. teach a method of instant claim 2, of detecting PCR-amplified base sequences wherein Schollen et al. disclose that the method comprises (i) conducting PCR amplification by mixing a plurality of pairs of primers with a sample (see page 19, column 1, paragraph 3), said primers being suitable for amplifying different base sequences of a same or different lengths by PCR (see page 19, Table 1, see fragment lengths); (ii) conducting a hybridization reaction by using a substrate on which one primer (RBD primer used as a PCR primer) of each said PCR primer pairs are fixed, and a hybridization solution containing said PCR amplified sequences (see page 19, column 1, paragraph 3, column 2, paragraph 1); detecting the hybridization spot on the substrate in which hybridization reaction occurred by

processing the entry of the fluorescent material using chemiluminscent kit (see page 19, column 2, paragraph 1). Schollen et al. also disclose the oligonucleotides on the substrate are equivalent to the PCR primers used in the amplification (see page 20, paragraph 1, column 2, paragraphs 1-4). With regard to the instant claim 4, Schollen et al. teach that the said PCR primers comprise a base length number ranging from 10-30 (see page 19, table 1, page 20, table 2). Although Schollen et al. teach a fluorescent intercalating dye reagent for detection of PCR amplified product on a gel electrophoresis, Schollen et al. did not teach specifically an intercalating agent as a fluorescent material used in hybridization assay.

Wittwer et al. teach a method of detecting an amplified target nucleic acid by processing an intercalating dye such as SYBR Green I, to enter in said target molecules comprising double-stranded DNA and detecting fluorescence excitation from said intercalating dye bound to the double-stranded DNA (see column 4, lines 51-57, column 23, lines 17-24, column 32, lines 52-67).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the method of detecting PCR-amplified base sequences as taught by Schollen et al. with the method of detection of double-stranded DNA using intercalating dye as taught by Wittwer et al. which is applicable to monitor a fluorescent signal from intercalating dye when bound to a double-stranded DNA because Wittwer et al. taught that double-strand- specific intercalating dyes show superior sensitivity, greater discrimination between double-stranded and single-stranded nucleic acid and inexpensive to use (see column 23, lines 17-24). An ordinary practitioner would have been motivated to combine the method of Schollen et al. with the method of detection of fluorescence signal from a double-stranded DNA

for the advantages of developing a cost-effective method for detecting PCR-amplified base sequences because inclusion of such limitation would reduce the use of expensive fluorescent labeling material in the detection of a target nucleic acid molecule.

Conclusion

No claims are allowable.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suryaprabha Chunduru whose telephone number is 571-272-0783. The examiner can normally be reached on 8.30A.M. - 4.30P.M, Mon - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's

supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and - for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Suryaprabha Chunduru
March 31, 2004

JEFFREY FREDMAN
PRIMARY EXAMINER